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(54) Title: RAPIDLY DISPERSING SOLID ORAL COMPOSITIONS

(57) Abstract: The present invention relates to the rapidly dispersing solid oral compositions comprising Olanzapine or Ondansetron. The present invention further discloses the wet granulation or direct compression method of producing such rapidly dispersing compositions. The pharmaceutically accepted solvate, salts, enantiomers or mixtures thereof including racemic mixture of Olanzapine and Ondansetron are contemplated to be within the scope of the present invention.

RAPIDLY DISPERSING SOLID ORAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to the rapidly dispersing solid oral composition and process for manufacture of such compositions.

DESCRIPTION OF THE RELEVANT ART

Oral administration in the form of a conventional tablet, pill or capsule constitutes the generally preferred route for administration of pharmaceuticals since this route is generally convenient and acceptable to patients. Unfortunately such compositions may be associated with certain disadvantages, particularly in the treatment of pediatric or geriatric patients, who may dislike or have difficulty in swallowing such compositions, or where administration of a conventional tablet, pill or capsule is not feasible.

In case of patients with psychosis and other mental disorders the administration of conventional solid dosage form is not always suitable due to patient compliance. In case of disorders where water intake needs to be limited or patients have reduced tendency to drink water for eg. Nausea, the use of rapidly dispersing tablet is suitable choice as it can be swallowed without water and disintegrates rapidly when it enters stomach.

U.S. Pat. No. 5,955,488 and 6,063,802 discloses that the Ondansetron hydrochloride dihydrate has bitter taste. In order to solve this problem the patents teaches the use of Ondansetron base in the form of freeze dried dosage form for oral administration. However, such freeze dried dosage form suffers from various drawbacks such as moisture sensitivity, inherent fragility and such like. This causes most of the operations like embossing, packing and handling of such product a difficult and cumbersome operation. In particular, it has been determined that, due to the inherent fragility, surface undulation, moisture sensitivity and chemical makeup of freeze-dried dosage forms, the application of compression for the purpose of embossing would cause deformation, reduced porosity and hence increased dispersion time, and possibly cracking of the dosage forms. Similarly, it is believed that the chemical makeup, moisture sensitivity, porosity and surface undulation of freeze dried dosage forms would cause ink to dissolve the dosage forms at the point of contact or to diffuse throughout the dosage forms leading to clarity problems. The said freeze dried products are also generally not suited for packing and handling

operations.

There have been commercialized rapidly dispersing tablets prepared by lyophilizing solutions containing various drugs (U.S.Pat.Nos.5,631,023) e.g., Pepcid® RPD (famotidine preparation, Merck). However, these tablets have the disadvantage in that the productivity of the process for the preparation thereof is very low because the process involves the steps of injecting a drug solutions into a pre-formed container, lyophilizing and coating the lyophilized product with an expensive material.

The said lyophilization and freeze dried technologies are substantially expensive and require sophisticated technologies. In order to overcome above disadvantages various alternative technologies has been tried in past.

Instead of lyophilization, Yamanouch Pharmaceutical Co. Ltd. has disclosed into WO 99/47126 a rapidly dispersing tablet prepared by using a water-soluble non saccharide polymer as a binder together with an active ingredient; and humidifying the tablet. Further, WO 93/12769 discloses a rapidly dispersing tablet prepared by filling a mold with a suspension containing an active ingredient together with agar and sugar; and drying the suspension to remove the solvent at 30°C in a vacuum. However, these processes suffer from low productivity and uneven product quality.

Cima labs has developed Orasolv technique which is disclosed in U.S.Pat.No. 6,024,981. Among the tablets prepared thereby, Zomig® Rapimelt (zolmitriptan preparation, Astrazeneca) has been commercialized. This tablet contains an effervescent substance but has the problems of incomplete disintegration in the oral cavity and displeasing effect of the effervescent gas generated in the oral cavity.

U.S.Pat.No. 3,885,026 discloses porous tablets prepared by adding a volatilizable adjuvant, e.g., urethane urea, ammonium carbonate or naphthalene, to other tablets components; tableting the resulting mixture; and heating the tablets to volatilize the adjuvant. However, a residual amount of the adjuvant in the tablet may generate a deleterious effect on the patient.

U.S.Pat.No.4,134,943 discloses porous tablets prepared by adding a liquid having a freezing

temperature in the range of -30 to 25°C to other tablet components; cooling the mixture below the freezing temperature to solidify the liquid; tableting the cooled mixture; and then evaporating the liquid. However, this process suffers from low productivity.

Accordingly, it is an object of the present invention to provide a rapidly dispersing solid oral composition comprising Ondansetron, Olanzapine along with pharmaceutically accepted salts, solvates, enantiomers or mixtures thereof including racemic mixture and method of producing such compositions.

SUMMARY OF THE INVENTION

The invention relates to the rapidly dispersing compositions and method of producing such compositions. The present invention uses substantially simple and cost effective manufacturing technique. The rapidly dispersible tablets prepared by such process has acceptable stability as per ICH guidelines and dispersed within 30 seconds preferably within 10 seconds and more preferably within 5 seconds. The rapidly dispersible compositions obtainable according to the invention, in addition to being dispersed rapidly have the following further advantages:

- It has substantially good organoleptic characteristics;
- It is devoid of any need for the cautions and measures required during handling and packaging of the freeze dried formulations;
- It avoids the use of organic solvents which might pose environmental safety problems

According to one of the embodiments of the invention the active ingredient along with one or more pharmaceutical excipients was blended for 5-10 minutes, the powder blend thus obtained was granulated with solution of wetting agent/surfactant in water, the wet mass thus obtained was sieved to obtain granules. The granules after drying were compressed into the tablets. Alternatively the tablets can be prepared using direct compression technique.

DETAILED DESCRIPTION OF THE INVENTION

The present invention therefore provides the rapidly dispersing tablet formulation for oral administration comprising an active ingredient, in the form of its free base or pharmaceutically accepted salts, solvate, enantiomers or mixtures thereof including racemic mixture and one or more pharmaceutically accepted excipients.

As used in this description and in the appended claims the word "rapidly dispersing" refers to the dosage form which disperses in water within 30 seconds, preferably within10 seconds and more

preferably within 5 seconds or less as per the test specified in United State Pharmacopoeia.

In the description and in the appended claims the word "pharmaceutically active ingredient" refers to any of the drug selected from ondansetron, olanzapine or pharmaceutically accepted salts, solvate, enantiomers or mixtures thereof including racemic mixture.

The term "pharmaceutically accepted excipients" as used in this description and in the appended claims comprise binders, dispersing agents, fillers, flavoring agents, sweetening agents, lubricants or glidants and such like. The "dispersing agent" in accordance with the present invention comprises crosscarmellose sodium, crosscarmellose calcium, crosspovidone, sodium starch glycolate, sodium carboxymethyl cellulose, hydroxypropylcellulose, xanthan gum, alginic acid and alginates one or more clays selected from bentonite, hectorite, magnesium aluminium silicate, and such like, preferably the dispersing agent used in the present invention is crosspovidone.

The "binders" used in the present invention are selected from gelatin, pregelatinized starch, starch paste, starch DC, starch 1500, acacia, tragacanth, guar gum, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, glucose, sucrose, sorbitol, polyvinylpyrrolidone plasdone S-630 and such like. The preferred binder of the present invention is pregelatinized starch.

Suitable "fillers" as used in this invention are selected from one or more starch derivatives selected from corn starch, potato starch or rice starch; one or more polysaccharides selected from the group consisting of dextrins or maltodextrins, microcrystalline cellulose, powdered cellulose, mixture of microcrystalline cellulose and guar gum, coprocessed blends of microcrystalline cellulose; one or more polyhydric alcohols selected from the group consisting of mannitol, xylitol, sorbitol and such like. The preferred fillers used in this invention are mannitol, microcrystalline cellulose and mixture of microcrystalline cellulose and guar gum.

The "surfactant or wetting agent" as used in this specification and in the appended claims is selected from any of polyoxyethylene sorbitan fatty acid esters, e.g., polyoxyethylene 20 sorbitan monolaurate (TWEEN 20), polyoxyethylene (4) sorbitan monolaurate (TWEEN 21), polyoxyethylene 20 sorbitan monopalmitate (TWEEN 40), polyoxyethylene 20 sorbitan monooleate (TWEEN 80); polyoxyethylene alkyl ethers, e.g., polyoxyethylene 4 lauryl

ether (BRIJ 30), polyoxyethylene 23 lauryl ether (BRIJ 35), polyoxyethylene 10 oleyl ether (BRIJ 97); and polyoxyethylene glycol esters, e.g., poloxyethylene 8 stearate (MYRJ 45), poloxyethylene 40 stearate (MYRJ 52) or mixtures thereof, or sodium lauryl sulphate and such like. The preferred surfactant of the present invention is sodium lauryl sulphate.

The suitable "lubricants" are talc, magnesium stearate, stearic acid or glyceryl behenate preferably magnesium stearate and suitable glidants includes colloidal silicon dioxide or talc preferably colloidal silicon dioxide.

Suitable "sweeteners" include, for example, sugars such as sucrose, lactose and glucose; cyclamate and salts thereof; saccharin and salts thereof; and aspartame. Preferably the sweetener of the rapidly dispersing dosage form of the present invention is aspartame. Suitable flavoring agent include strawberry, cherry, mint and caramel flavouring aids, preferably the flavoring agent of the present invention is strawberry flavour.

Within the above preferred aspects of the invention, rapidly dispersing composition, wherein the amount of active ingredient is in the range of 1 to 25 mg. When the pharmaceutically active ingredient is Ondansetron or a free base, salt, solvate, enantiomer or mixture thereof including racemic mixture, the preferred amount is 4, 8, 16 or 24 mg. When the pharmaceutically active ingredient is Olanzapine or a free base, salt, solvate, enantiomer or mixture thereof including racemic mixture, the preferred amount is 5, 10, 15 or 20 mg.

It is worth to mention that though examples given in the present description are limited to the particular amount of dosage form, it is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one know to the industry.

The following examples describe the present invention in detail but does not limit the invention in any way.

Example 1.

Ondansetron 4 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1.	Ondansetron	4
2.	Microcrystalline cellulose (Avicel 101)	16.5
3.	Mannitol	2.5
4.	Pregelatinized starch	2.5
5.	Crosspovidone	5
6.	Aspartame	2
7	Colloidal silicon dioxide	1
8	Magnesium stearate	0.5
9	Microcrystalline cellulose (Avicel 112)	12.85
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	2.5
11	Sodium lauryl sulphate	0.15
12	Strawberry Flavor	0.5

Preparation method:

1. Ingredients 1 to 4 and half quantity of ingredient 5 were weighed and passed through mesh #60 and blended for 5–10 minutes.
2. The powder blend obtained from step (1) was granulated with the solution of sodium lauryl sulphate (ingredient 11) in water to obtain wet mass.
3. The wet mass of step (2) was passed through mesh # 10 to obtain wet granules. The wet granules were dried at suitable temperature from 40^0C-65^0C till the LOD (Loss on drying) of the granules was 2% or less.
4. The dried granules of step (3) were passed through mesh # 30.
5. Ingredients 6 to 10, 12 and remaining half the quantity of ingredients 5 were weighed and passed through mesh # 40 and blended with dried granules obtained from step (4) to obtain lubricated blend.
6. The lubricated blend of step (5) was compressed to tablets using suitable punches.

5 Example 2.

Ondansetron 8mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Ondansetron	8
2	Microcrystalline cellulose (Avicel 101)	33
3	Mannitol	5
4	Pregelatinized starch	5
5	Crosspovidone	10
6	Aspartame	4
7	Colloidal silicon dioxide (Aerosil 200)	2
8	Magnesium stearate	1
9	Microcrystalline cellulose (Avicel 112)	25.7
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	5
11	Sodium lauryl sulphate	0.3
12	Strawberry Flavor	1

Procedure: Same as in example 1.

Example 3:

Ondansetron 24 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Ondansetron	24
2	Microcrystalline cellulose (Avicel 101)	60
3	Sorbitol	15
4	Plasdone S-630	10
5	Crosscarmellose sodium	27
6	Aspartame	10
7	Colloidal silicon dioxide (Aerosil 200)	6
8	Lubritalc	3
9	Microcrystalline cellulose (Avicel 112)	40.4
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	15
11	Tween 80	0.6
12	Strawberry Flavor	3

Procedure: Same as in example 1.

Example 4:

Ondansetron 4 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Ondansetron	4
2	Crosspovidone	33.86
3	Aspartame	1.5
4	Magnesium stearate	1
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	4
6	Sodium lauryl sulphate	0.135
7	Strawberry Flavor	0.5

Preparation method:

1. Ingredients 1 to 3 were weighed and passed through mesh #80 and blended for 5 – 10 minutes.
2. The blend obtained from step (1) was granulated with solution of sodium lauryl sulphate (ingredient 6) in water in FBP (fluid bed processor) and dried.
3. After completion of drying process, ingredients 4, 5, and 7 were charged in to the fluid bed processor and mixed for 3 minutes at 30^0C, to obtain a lubricated blend.
4. The lubricated blend of step (3) was passed through mesh # 40 and compressed into tablets using suitable punches.

Example 5.

Ondansetron 8mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Ondansetron	8
2	Crosspovidone	67.73
3	Aspartame	3
4	Magnesium stearate	2
5	Microcrystalline cellulose and Guar gum (Avicel CE 15	8
6	Sodium lauryl sulphate	0.27
7	Strawberry Flavor	1

Preparation method: Same as in example 4.

Example 6.

Ondansetron 24 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Ondansetron	24
2	Crosspovidone	70
3	Aspartame	9
4	Lubritalc	6
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	24
6	Tween 80	0.81
7	Strawberry Flavor	3

Same as in example 4.

Example 7.

Olanzapine 5 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	5
2	Microcrystalline cellulose (Avicel 101)	15.5
3	Mannitol	2.5
4	Pregelatinized starch	2.5
5	Crosspovidone	5
6	Aspartame	2
7	Colloidal silicon dioxide (Aerosil 200)	1
8	Magnesium stearate	0.5
9	Microcrystalline cellulose (Avicel 112)	12.85
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	2.5
11	Sodium lauryl sulphate	0.15
12	Strawberry Flavor	0.5

Preparation method:

The similar method as described in example 1 was adopted for the preparation of above mentioned tablets.

Example 8.

Olanzapine 10 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	10
2	Microcrystalline cellulose (Avicel 101)	10.5
3	Mannitol	2.5
4	Pregelatinized starch	2.5
5	Crosspovidone	5
6	Aspartame	2
7	Colloidal silicon dioxide (Aerosil 200)	1
8	Magnesium stearate	0.5
9	Microcrystalline cellulose (Avicel 112)	12.85
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	2.5
11	Sodium lauryl sulphate	0.15
12	Strawberry Flavor	0.5

Preparation method:

The similar method as described in example 1 was adopted for the preparation of above mentioned tablets.

Example 9.

Olanzapine 20 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	20
2	Microcrystalline cellulose (Avicel 101)	21
3	Sorbitol	5
4	Hydroxypropylmethylcellulose	5
5	Alginic acid and Sodium starch glycolate	12
6	Aspartame	4
7	Colloidal silicon dioxide (Aerosil 200)	2
8	Glyceryl behenate	1
9	Microcrystalline cellulose (Avicel 112)	25.7
10	Microcrystalline cellulose and Guar gum (Avicel CE 15)	5
11	Tween 80	0.3
12	Strawberry Flavor	1

Preparation method:

The similar method as described in example 1 was adopted for the preparation of above mentioned tablets.

Example 10.

Olanzapine 5 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	5
2	Crosspovidone	32.86
3	Aspartame	1.5
4	Magnesium stearate	1
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	4
6	Sodium lauryl sulphate	0.135
7	Strawberry Flavor	0.5

Preparation method:

The similar method as described in example 4 was adopted for the preparation of above mentioned tablets.

Example 11.

Olanzapine 10 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	10
2	Crosspovidone	27.86
3	Aspartame	1.5
4	Magnesium stearate	1
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	4
6	Sodium Lauryl Sulfate	0.135
7	Strawberry Flavor	0.5

Preparation method:

The similar method as described in example 4 was adopted for the preparation of above mentioned tablets.

Example 12.

Olanzapine 20 mg rapidly dispersing tablet:

SN	Ingredients	Quantity in mg
1	Olanzapine	20
2	Crosspovidone	55.73
3	Aspartame	3
4	Magnesium stearate	2
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	8
6	Sodium lauryl sulphate	0.27
7	Strawberry Flavor	1

Preparation method:

The similar method as described in example 4 was adopted for the preparation of above mentioned tablets.

It is obvious to those skilled in the art that both the methods of wet granulation and direct compression can be suitably and successfully applied for the preparation of the tablets as per any

of the examples 1 to 4. When direct compression method is used for the manufacture of tablets the water and sodium lauryl sulphate is not needed in the formulation which is exemplified by the following example.

Example 13.

Olanzapine/Ondansetron rapidly dispersing tablets:

SN	Ingredients	% W/W
1	Olanzapine/ Ondansetron	22.22
2	Crosspovidone	62.22
3	Aspartame	3.33
4	Magnesium stearate	2.22
5	Microcrystalline cellulose and Guar gum (Avicel CE 15)	8.88
6	Strawberry Flavor	1.11

Preparation procedure:

All the ingredients 1-6 are passed through mesh # 40 and blended in suitable blender for 5-10 minutes and compressed into tablets using suitable punches.

The examples given above are only meant to be explanatory and in no way limit the scope of the present invention. Many variation of the present invention, disclosed in the detailed description, are obvious to those skilled in the art and are contemplated to be within the scope of the present invention.

WE CLAIM:

1. Rapidly dispersing solid oral composition comprising Ondansetron or a pharmaceutically accepted salts, solvates, enantiomers or mixtures thereof including racemic mixture, in an amount of 1 mg to 25 mg, with at least one pharmaceutically accepted excipients selected from the group consisting of an at least one binder in an amount of 2% to 10%, an at least one dispersing agent in an amount of 5% to 15%, an at least one filler in an amount of 50% to 75%, an at least one glidants or lubricant in an amount of 0.5% to 5% and an at least one sweetener in an amount of 1% to 6%.
2. The composition of claim 1 comprising the binders selected from the group consisting of gelatin, pregelatinized starch, starch paste, starch DC, starch 1500, acacia, tragacanth, guar gum, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, glucose, sucrose, sorbitol, polyvinylpyrrolidone or plasdone S-630.
3. The composition of claim 1 comprising the dispersing agent selected from the group consisting of crosscarmellose sodium, sodium carboxymethyl cellulose, crosspovidone, sodium starch glycolate, hydroxypropylcellulose, hydroxypropylmethylcellulose, xanthan gum, alginic acid, alginates or bentonite.
4. The composition of claim 1 comprising the fillers selected from the group consisting of one or more starch derivatives selected from corn starch, potato starch or corn starch one or more polysaccharides selected from the group consisting of dextrins, maltodextrin, microcrystalline cellulose, powdered cellulose, mixture of microcrystalline cellulose and guar gum; one or more polyhydric alcohols selected from the group consisting of mannitol, xylitol or sorbitol.
5. The composition of claim 1 comprising the lubricants selected from talc, magnesium stearate, stearic acid or glyceryl behenate.
6. The composition of claim 1 comprising glidants selected from colloidal silicon dioxide or talc.
7. The composition of claim 1 comprising the sweeteners selected from group consisting of sugars such as sucrose, lactose or glucose; cyclamate or salts thereof; saccharin or salts thereof; or aspartame.
8. Rapidly dispersing solid oral pharmaceutical composition comprising ondansetron as free base, microcrystalline cellulose, pregelatinized starch, mannitol, crosspovidone, aspartame, mixture of microcrystalline cellulose and guar gum, sodium lauryl sulphate, colloidal silicon dioxide and magnesium stearate.

9. Rapidly dispersing solid oral pharmaceutical composition comprising Ondansetron as free base, crosspovidone, aspartame, mixture of microcrystalline cellulose and guar gum, sodium lauryl sulphate and magnesium stearate.
10. Rapidly dispersing solid oral composition comprising Olanzapine or a pharmaceutically accepted salts, solvates, enantiomers or mixtures thereof including racemic mixture, in an amount of 1 mg to 25 mg, with at least one pharmaceutically accepted excipients selected from the group consisting of an at least one binder in an amount of 2% to 10%, an at least one dispersing agent in an amount of 5% to 15%, an at least one filler in an amount of 50% to 75%, an at least one glidants or lubricant in an amount of 0.5% to 5% and an at least one sweetener in an amount of 1% to 6%.
11. The composition of claim 10 comprising the binders selected from the group consisting of gelatin, pregelatinized starch, starch paste, starch DC, starch 1500, acacia, tragacanth, guar gum, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, glucose, sucrose, sorbitol, polyvinylpyrrolidone or plasdone S-630.
12. The composition of claim 10 comprising the dispersing agent selected from the group consisting of crosscarmellose sodium, sodium carboxymethyl cellulose, crosspovidone, sodium starch glycolate, hydroxypropylcellulose, hydroxypropylmethylcellulose, xanthan gum, alginic acid, alginates or bentonite.
13. The composition of claim 10 comprising the fillers selected from the group consisting of one or more starch derivatives selected from corn starch, potato starch or rice starch one or more polysaccharides selected from the group consisting of dextrins, maltodextrin, microcrystalline cellulose, powdered cellulose, mixture of microcrystalline cellulose and guar gum; one or more polyhydric alcohols selected from the group consisting of mannitol, xylitol or sorbitol.
14. The composition of claim 10 comprising the lubricants selected from talc, magnesium stearate, stearic acid or glyceryl behenate.
15. The composition of claim 10 comprising glidants selected from colloidal silicon dioxide or talc.
16. The composition of claim 10 comprising the sweeteners selected from group consisting of sugars such as sucrose, lactose or glucose; cyclamate or salts thereof; saccharin or salts thereof; or aspartame.
17. Rapidly dispersing solid oral pharmaceutical composition comprising Olanzapine as free base, microcrystalline cellulose, pregelatinized starch, mannitol, crosspovidone, aspartame,

mixture of microcrystalline cellulose and guar gum, sodium lauryl sulphate, colloidal silicon dioxide and magnesium stearate.

18. Rapidly dispersing solid oral pharmaceutical composition comprising Olanzapine as free base, crosspovidone, aspartame, mixture of microcrystalline cellulose and guar gum, sodium lauryl sulphate and magnesium stearate.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/4178 A61K31/5513

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 57857 A (YUHAN CORP) 5 October 2000 (2000-10-05) example 5; table 1.1	1-7
Y	---	1-18
X	US 6 190 698 B1 (MORRIS TOMMY CLIFFORD ET AL) 20 February 2001 (2001-02-20) column 4, line 63 -column 5, line 11 examples 1,2	10-15
Y	---	1-18
Y	WO 99 47126 A (CHU JAMES SHUNNAN ;YAMANOUCHI SHAKLEE PHARMA (US); LIU FANG YU (US) 23 September 1999 (1999-09-23) cited in the application page 2, line 24 -page 4, line 15 page 14, line 1 -page 15, line 14 example 1	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2002	13/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giménez Miralles, J

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